

Claims:

- c 2*
1. (Currently Amended) An injectable pharmaceutical composition comprising:
an aqueous suspension of microdroplets suitable for intravenous delivery, the
microdroplets having a mean diameter between 200 Angstroms and one micron, the
microdroplets comprising a substantially water-insoluble, pharmacologically acceptable
lipophilic liquid vehicle with at least one membrane-forming lipid and [that does not tend to
form micelle structures,] a camptothecin dissolved in the lipophilic liquid vehicle [water-
insoluble, and pharmacologically acceptable liquid], and an outer layer comprising a
phospholipid.
 2. (Original) An injectable pharmaceutical composition according to claim 1 wherein the
camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-
20(S)-camptothecin, 9-methyl-camptothecin, 9-chloro-camptothecin, 9-flouro-camptothecin,
7-ethyl camptothecin, 10-methyl-camptothecin, 10-chloro--camptothecin, 10-bromo-
camptothecin, 10-fluoro-camptothecin, 9-methoxy-camptothecin, 11-fluoro-camptothecin, 7-
ethyl-10-hydroxy camptothecin, 10,11-methylenedioxy camptothecin, and 10,11-
ethylenedioxy camptothecin, and 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy
camptothecin.
 3. (Original) An injectable pharmaceutical composition according to claim 1 wherein the
camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-
20(S)-camptothecin, 7-ethyl-10-(4-(1-piperdino)-1-piperdino)-carbonyloxy-camptothecin, 7-
ethyl-10-hydroxy-20(S)-camptothecin, 10,11-methylenedioxy-20(S)-camptothecin, 9-chloro-
20(S)-camptothecin, 9-bromo-20(S)-camptothecin, 9-hydroxy-20(S)-camptothecin, and 11-
hydroxy-20(S)-camptothecin.
 4. (Original) An injectable pharmaceutical composition according to claim 1 wherein the
camptothecin is 9-nitro-20(S)-camptothecin.
 5. (Original) An injectable pharmaceutical composition according to claim 1 wherein the
pharmaceutical composition has a pH less than 7.

Application No. 09/782,184
Amendment Dated July 22, 2003
Reply to Office Action of January 22, 2003

6. (Original) An injectable pharmaceutical composition according to claim 1 wherein the pharmaceutical composition has a pH less than 6.

C 1
Cont

7. (Original) An injectable pharmaceutical composition according to claim 1 wherein the pharmaceutical composition has a pH between 5 and 6.

8. (Original) An injectable pharmaceutical composition according to claim 1 wherein the pharmaceutical composition comprises an isotonic solution.

9. (Original) An injectable pharmaceutical composition according to claim 1 wherein the pharmaceutical composition comprises mannitol or trehalose.

10. (Original) An injectable pharmaceutical composition according to claim 1 wherein the composition has been thermally sterilized.

11. (Original) An injectable pharmaceutical composition according to claim 1 wherein the composition has been thermally sterilized by heating to at least 121°C for at least 15 minutes.

12. (Original) An injectable pharmaceutical composition according to claim 1 wherein the pharmaceutically acceptable organic liquid is selected from the group consisting of alkanes, dialkyl ethers, long-chain esters, hydrophobic esters, biocompatible silicones, biocompatible high molecular weight fluorocarbons, oil-soluble vitamins and volatile liquid anesthetics.

13. (Original) An injectable pharmaceutical composition according to claim 1 wherein the camptothecin is present in amounts of up to about 25% w/w.

14. (Original) An injectable pharmaceutical composition according to claim 1 wherein the camptothecin is present in amounts of from about 0.05% w/w to about 5% w/w.

15. (Original) An injectable pharmaceutical composition according to claim 1 wherein the camptothecin is present in amounts of from about 0.1% w/w to about 1% w/w.

16. (Original) An injectable pharmaceutical composition according to claim 1 wherein the camptothecin is present in amount of about 0.2% w/w.

c 2
cont

17. (Original) An injectable pharmaceutical composition according to claim 1 wherein the camptothecin is present in amounts of up to about 5% w/w.

18. (Currently Amended) An injectable pharmaceutical composition comprising:
a dispersion in an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents and liquid droplets having a size range of micrometer to submicrometer, the droplets comprising
a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid vehicle with at least one membrane-forming lipid [that does not tend to form micelle structures] and a camptothecin dissolved in the lipophilic liquid vehicle, and
an outer layer surrounding the droplet comprising at least one membrane-forming amphipathic lipid,
wherein upon thermal sterilization the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm .

19. (Currently Amended) An injectable pharmaceutical composition comprising:
an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents;
a dispersion of liquid droplets of a first size distribution, the liquid droplets comprising
a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid vehicle [that does not tend to form micelle structures],
solid particles of a camptothecin of a second size distribution, and
an outer layer surrounding the droplet comprising at least one membrane-forming amphipathic lipid;

wherein the first size distribution is in the range of submicrometer to micrometers, and the second size distribution is smaller than the first size distribution; and

wherein upon thermal sterilization, the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm .

C 1
Cont

20. (Original) An injectable pharmaceutical composition according to claim 18 wherein the membrane-forming amphipathic lipid comprises a phospholipid.

21. (Original) An injectable pharmaceutical composition according to claim 20 wherein the phospholipid is selected from the group consisting of saturated phospholipids, unsaturated phospholipids, synthetic phospholipids, natural phospholipids, and combinations thereof.

22. (Previously Presented) An injectable pharmaceutical composition according to claim 20 wherein the phospholipid is selected from the group consisting of natural and synthetic lipids, hen egg-derived phospholipid, egg phospholipid, purified egg phospholipid, soy phospholipid, dimyristoyl lecithin, didodecanoyl lecithin, dioeoyl lecithin, dilinoeoyl lecithin, alpha-palmito-beta-oleoyl lecithin, alpha-palmitoyl-beta-linoleoyl lecithin, alpha-oleoyl-beta-palmitoyl lecithin, diarachidonyl lecithin, alpha-palmito-beta-myristoyl lecithin, dimyristoyl phosphatidic acid, dipalmitoyl phosphatidic acid, distearoyl phosphatidic acid, phosphatidyl serine, phosphatidyl inositol, dimyristoyl phosphatidyl glycerol, dipalmitoyl phosphatidyl glycerol, dioctadecanoyl phosphatidyl ethanolamine, dioleoyl phosphatidyl ethanolamine, dihexadecyl phosphatidyl ethanolamine, dilauryl phosphatidyl ethanolamine, dimyristoyl phosphatidyl ethanolamine and dipalmitoyl phosphatidyl ethanolamine.

23. (Previously Presented) An injectable pharmaceutical composition according to claim 20 wherein the phospholipid comprises egg phospholipid.

24. (Original) An injectable pharmaceutical composition according to claim 18 wherein the outer layer further comprises cholesterol.

Application No. 09/782,184
Amendment Dated July 22, 2003
Reply to Office Action of January 22, 2003

25. (Original) An injectable pharmaceutical composition according to claim 18 wherein the membrane-forming amphipathic lipid is present in amounts of from 0.2% w/w to about 5% w/w.

26. (Original) An injectable pharmaceutical composition according to claim 18 wherein the membrane-forming amphipathic lipid is present in amounts of from 1% w/w to about 5% w/w.
*Q1
Cont*

27. (Original) An injectable pharmaceutical composition according to claim 18 wherein the membrane-forming amphipathic lipid is present in amounts of about 4% w/w.

28. (Original) An injectable pharmaceutical composition according to claim 18 wherein the lipophilic liquid vehicle is selected from the group consisting of vegetable oils, animal oils, synthetic oils, semi-synthetic oils, soybean oil, medium chain triglycerides, long chain triglycerides, triglycerides of C8 to C12 saturated fatty acids, triglycerides of C14 to C22 saturated fatty acids, triglycerides of C14 to C22 unsaturated fatty acids, and combinations thereof.

29. (Original) An injectable pharmaceutical composition according to claim 18 wherein the lipophilic liquid vehicle is selected from the group consisting of soybean oil, triglycerides of C8 to C12 saturated fatty acids, and combinations thereof.

30. (Original) An injectable pharmaceutical composition according to claim 18 wherein the lipophilic liquid and the membrane-forming amphipathic lipid further comprise cholesterol.

31. (Previously Presented) An injectable pharmaceutical composition according to claim 18 wherein the camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-20(S)-camptothecin, 9-methyl-camptothecin, 9-chloro-camptothecin, 9-fluoro-camptothecin, 7-ethyl camptothecin, 10-methyl-camptothecin, 10-chloro-camptothecin, 10-bromo-camptothecin, 10-fluoro-camptothecin, 9-methoxy-camptothecin, 11-fluoro-camptothecin, 7-ethyl-10-hydroxy camptothecin, 10,11-methylenedioxy

Application No. 09/782,184
Amendment Dated July 22, 2003
Reply to Office Action of January 22, 2003

camptothecin, and 10,11-ethylenedioxy camptothecin, and 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy camptothecin.

32. (Previously Presented) An injectable pharmaceutical composition according to claim 18 wherein the camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-20(S)-camptothecin, 7-ethyl-10-(4-(1-piperdino)-1-piperdino)-carbonyloxy-camptothecin, 7-ethyl-10-hydroxy-20(S)-camptothecin, 10,11-methylenedioxy-20(S)-camptothecin, 9-chloro-20(S)-camptothecin, 9-bromo-20(S)-camptothecin, 9-hydroxy-20(S)-camptothecin, and 11-hydroxy-20(S)-camptothecin.

*C2
Cont*

33. (Previously Presented) An injectable pharmaceutical composition according to claim 18 wherein the camptothecin is 9-nitro-20(S)-camptothecin.

34. (Previously Presented) An injectable pharmaceutical composition according to claim 19 wherein the camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-20(S)-camptothecin, 9-methyl-camptothecin, 9-chloro-camptothecin, 9-fluoro-camptothecin, 7-ethyl camptothecin, 10-methyl-camptothecin, 10-chloro-camptothecin, 10-bromo-camptothecin, 10-fluoro-camptothecin, 9-methoxy-camptothecin, 11-fluoro-camptothecin, 7-ethyl-10-hydroxy camptothecin, 10,11-methylenedioxy camptothecin, and 10,11-ethylenedioxy camptothecin, and 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy camptothecin.

35. (Previously Presented) An injectable pharmaceutical composition according to claim 19 wherein the camptothecin is selected from the group consisting of 9-nitro-20(S)-camptothecin, 9-amino-20(S)-camptothecin, 7-ethyl-10-(4-(1-piperdino)-1-piperdino)-carbonyloxy-camptothecin, 7-ethyl-10-hydroxy-20(S)-camptothecin, 10,11-methylenedioxy-20(S)-camptothecin, 9-chloro-20(S)-camptothecin, 9-bromo-20(S)-camptothecin, 9-hydroxy-20(S)-camptothecin, and 11-hydroxy-20(S)-camptothecin.

36. (Previously Presented) An injectable pharmaceutical composition according to claim 19 wherein the camptothecin is 9-nitro-20(S)-camptothecin.

Application No. 09/782,184
Amendment Dated July 22, 2003
Reply to Office Action of January 22, 2003

Drawings:

The drawings in this application were objected to in the Office Action by the Examiner under 37 C.F.R. §1.84(g), left margins not acceptable. Accordingly, Applicants submit herewith new revised Figures 1-16.

Attachment: Replacement Figures 1-16